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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/471,622	06/05/95	HUSE	

EXAMINER	
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ART UNIT	PAPER NUMBER
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DATE MAILED: 1646
03/20/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 12/08/98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-33, 66-81 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-33, 66-81 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-33, 66-81 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

1) Claims 1 to 33 and 66 to 81 are pending in the instant application. Claims 1, 9 and 11 to 13 have been amended, claims 34 to 65 have been canceled and claims 80 and 81 have been added as requested by Applicant in Paper Number 11, filed 08 December of 1998.

2) Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4) The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1646.

5) Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1 to 8, 16 to 33, and 76 to 81, drawn to a plurality of expression vectors, a cloning system for making these vectors, and cells transformed therewith, classified in Class 435, subclass 252.3.

II. Claims 9 to 15, and 66 to 75, drawn to a vector and a kit for the preparation of vectors encoding heteromeric receptor proteins, classified in Class 435, subclass 69.1.

Inventions II and I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). In the instant case the vectors of invention II could be used in a plurality of different cloning projects unrelated to the generation of

a cell population containing diverse combinations of receptors.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6) Claims 1, 3 to 5, and 80 are rejected under 35 U.S.C. § 101 because they are drawn to non-statutory subject matter. These claims read on a population of T or B lymphocytes as they occur in a mammalian system and which are not patentable. As currently used in the art the term "fusion protein" would include any protein encoded by a member of the immunoglobulin gene superfamily.

7) Claims 6 to 8 are rejected under 35 U.S.C. § 101 because they are drawn to a nonfunctional invention. These claims further limit claim 1 in requiring the plurality of cells to produce bacteriophage without limiting these cells to bacterial cells.

8) Claims 1 to 33 and 68 to 75 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1 to 33 and 68 to 75 of copending Application No. 08/470,297. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

9) Claims 1 to 8 and 16 to 33 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 to 8, 16 to 21 and 23 to 33 of copending Application No. 08/349,131. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the instant application completely encompass the subject matter claimed in claims 1 to 8, 16 to 21 and 23 to 33 of copending Application No. 08/349,131.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10) Claims 1 to 33 and 66 to 81 are rejected under 35 U.S.C. 112, first paragraph, as

based on a disclosure which is not enabling. Claims which omit numerous elements which are critical or essential to the practice of the invention, but not included in the claims are not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

The instant specification discloses the construction and use of a specific pair of expression vectors which can be employed in a disclosed method of obtaining the incorporation of two different proteins into a single chimeric protein through an efficient mechanism of gene fusion and the expression of that chimeric protein on the surface of a host. This system is illustrated in Figure 1 of the instant application and explained in detail in the text on pages 8 to 12 therein. It is indisputably clear from this text that a first and second vector of the instant invention each need considerably more than the "two pairs of restriction sites symmetrically oriented about a cloning site and in an identical orientation", which is the only material limitation recited in the claims. Each of claims 1, 80 and 81, for example, essentially recite nothing more than a desired conclusion without reciting those material elements needed to achieve that conclusion. These claims constitute nothing more than a wish to know the identity of any composition with the recited features. The text beginning in the first full paragraph on page 8 of the instant specification teaches that one of the vectors must encode a portion of a structural gene needed to obtain the expression of heterologous gene on the surface of a host and that the second vector must contain elements which are also needed for that expression and which are lacking from the first vector. It is clear that viability upon recombination is required to use the vectors of the instant invention but the instant claims do not materially reflect this element. In other words, it would appear that neither vector should have the ability to produce a viable bacteriophage unless it has been combined with the second vector if they are to be used as described in the instant

specification and yet the instant claims do not recite material limitations which would result in this necessary functional limitation. There is no disclosure or guidance at all in the instant specification which would permit an artisan to practice the instant invention outside of the context of a filamentous bacteriophage.

The instant specification is only enabling for the production of single chain binding antibodies, each consisting of a single fusion protein comprising an antibody variable light chain, an antibody variable heavy chain and a surface protein from a host cell. The instant application provides absolutely no guidance in the production of a cell or phage which expresses a first and second polypeptide separately. The instant specification is also completely devoid of any description of a method of obtaining the expression of a polypeptide on the surface of a host without that polypeptide being part of a chimeric protein which also contains a surface protein from that host. As explained below, the expression of single chain antibodies composed of variable light and variable heavy antibody chains on the surface of a host to permit the isolation of DNAs encoding single chain antibodies with desired binding properties was known in the art prior to the making of the instant invention. The PCR amplification and isolation of DNAs encoding variable light and heavy chains of antibodies was also known and practiced in the art at that time. As explained on pages 5 and 6 of the instant specification, the novelty of the instant invention is the provision of a two vector system which permits the efficient incorporation of a DNA encoding a single variable light chain of an antibody and a single variable heavy chain of an antibody into an expression system in which the DNAs are incorporated at random from a population of DNAs encoding different variable heavy and variable light chains. These DNAs are invariably expressed as single chain antibodies which are

initially fused to a surface protein of the host producing them. None of the instant claims reflect those material limitations which provide the novel aspects of the invention which is disclosed in the instant specification and which are essential to the practice of that invention.

It is further noted that the instant specification does not disclose any manner of obtaining the expression of a heterologous fusion protein on the surface of a host without the need to provide two copies of a gene encoding the surface protein which has been employed to display that heterologous proteins. The first copy is expressed as a nonchimeric protein which is essential to the structural integrity of the bacteriophage host and the second copy is employed to obtain the surface display of the heterologous protein Such vectors would also require other elements such as an origin of replication and at least one selectable marker in each to permit its propagation in a bacterial host. As stated above, there are numerous material elements which are needed for a pair of vectors to be employed in the process that is disclosed in the instant specification and the instant claims lack these material elements.

The claims 9 to 15 essentially contain two elements. The first is that the claimed kit is "for the preparation of vectors for the coexpression of two DNA sequences encoding polypeptides". The second limitation is that the claimed kit contain two expression vectors, each having "two pairs of restriction sites symmetrically oriented about a cloning site". The claims do not require the two vectors to differ from one another nor do the claims recite a material element or combination of elements which distinguishes the first vector from the second vector. The omission of this material element or combination of elements from the claims renders them both incomplete and vague and indefinite. Claim 11 further requires that "said coexpression is as a fusion protein on the surface of

a cell". There are no material element in this claim or any of the claims from which it depends which would result in the expression of a fusion protein on the surface of a cell. Claim 11 recites a desired function without reciting those material elements which are required to provide that function. Claim 12 requires a cell to produce filamentous bacteriophage and yet the claims do not recite any element which reflects a relationship between the claimed kit and this ability of a host cell to produce filamentous bacteriophage. Claim 14 requires one of the expressed sequences to be expressed as a fusion protein "with gene VIII". There is no antecedent basis for "gene VIII" and the claims do not require either of the vectors of the claimed kit to encode a "gene VIII" product. Further, the orientation of the "polypeptide" within a fusion protein containing the gene VIII product of the bacteriophage M13 is critical to the practice of the instant invention and this orientation is not recited in the instant claims.

Further, the disclosure is enabling only for claims limited to first and second DNA sequences encoding the functional portions of the variable heavy and variable light chains of an antibody molecule. See M.P.E.P. §§ 706.03(n) and 706.03(z). The instant specification is not enabling for the practice of the instant invention with any other DNA sequences encoding any other heteromeric receptors. The PCR primers described in the instant specification appear to be critical for the practice of the instant invention. The specification does not list such primers or identify art listing such primers for any heteromeric binding proteins other than those composed of the variable heavy and light chains of immunoglobulins.

11) Claims 6 to 8 are rejected under 35 U.S.C. § 112, first paragraph, because the instant specification does not provide the guidance needed to produce bacteriophage in a cell which is not

bacterial.

12) Claims 1 to 33 and 66 to 81 are rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential elements as explained above, such omissions amounting to gaps between the elements. See MPEP § 2172.01.

12.1) Claims 6 to 8, 22 to 24, and 31 to 33 are confusing because they do not indicate that there is any functional relationship between the recited bacteriophage, the DNA encoding the heteromeric receptors and the cells producing them. Applicant has traversed this rejection on the premise that "claims 6, 22 and 31, respectively, depend on claims 77-79". No, they don't. Applicant is encouraged to carefully review the claims at issue before making any further response to this rejection.

12.2) Claim 26 is confusing in effectively claiming a plurality of polypeptides forming a single receptor which binds a single molecule. Claims 29 to 33 are indefinite only in that they depend from claim 26. Applicant has traversed this rejection on the premise that "the claim is sufficiently clear to enable one skilled in the art to practice the invention"!!! Applicant is advised that a rejection under 35 U.S.C. § 112, second paragraph, has nothing to do with enablement and everything to do with the clarity of the claims. Claim 26 lacks clarity because it is confusing for those reasons of record.

12.3) Claim 81 is vague and indefinite in referring to "possible" first and second DNA sequences because one can not determine what is included and excluded by this term.

13) Claims 9 to 14 are rejected under 35 U.S.C. § 102(b) because they encompass a kit containing any one of a plurality of bacterial cloning which were old, well known and in routine use

in the art more than a year before the making of the instant invention. Because the claims do not recite a difference between the first and second vectors of the instant invention, they encompass any kit containing a single vector. Because nucleic acid vectors are invariably stored in containers, any description of a vector would constitute a description of a kit containing that vector. Claim 11 is not distinguishing because it places no actual material limitation on the claimed kit. It is a matter of law that "functional statements therein do not limit article claims" (*In re Hutchison*, 69 USPQ 138, CCPA 1947). Claim 11 actually recites nothing more than a potential use for the vector of claim 9. Any bacterial expression vector meets the additional limitations of claims 11 to 13 because the functional limitations recited therein do not materially further limit the vector of claim 9. Any bacterial vector can be propagated in a host which also happens to produce a bacteriophage. Any expression vector can receive a DNA encoding a fusion protein. Because the only material limitations of the instant claims are met by any kit containing an expression vector containing "two pairs of restriction sites symmetrically oriented about a cloning site and in an identical orientation" they encompass such well known cloning vectors as lambdaGEM-11™, lambdaGEM-12™, M13mp7 and pUC7, for example. A copy of the sequence of the multiple cloning site from M13mp7 and pUC7 is was provided with Paper Number 13 of copending Application No. 08/470,297 for Applicant's consideration. This sequence was copied from a 1988 "UNITED STATES BIOCHEMICAL CORPORATION" catalog of enzymes and reagents for molecular biology. Applicant is advised that symmetric cloning sites like those present in M13mp7 and pUC7 were also present in all of the pUC vectors preceding pUC7, but no effort will be made to identify every prior art vector encompassed by the instant claims.

14) Claims 1 to 5 and 25 to 30 stand rejected under 35 U.S.C. § 103 as being unpatentable

over the Huse et al. publication (Science 246:1275-1281, 1989) in view of the Ladner et al. publication (WO 88/06630, 1988). The subject of these claims differs from the cells, vectors, and cloning system disclosed in the Huse et al. reference in having the receptor protein of the instant invention expressed on the surface of a host cell as opposed to that disclosed in the Huse reference which is confined to the host cell cytoplasm. Applicant has not identified the error in this showing. Applicant's observation that neither Ladner et al. or Huse et al. did not disclose the surface expression of two polypeptides which form heteromeric receptors on the surface of a cell is incorrect. The only disclosure in the instant specification of "the surface expression of two polypeptides which form heteromeric receptors on the surface of a cell" is the expression of single chain antibodies on the surface of a bacteriophage as part of a singe fusion protein which also includes a surface protein from that bacteriophage. The Ladner et al. reference has been relied upon because it shows that the expression of an antibody derived binding protein identified therein as a single chain antibody (SCA), which is composed of a VH and VL chain, on the surface of a recombinant host organism to allow for the identification of those host organisms carrying DNA sequences encoding binding proteins with the desired binding characteristics was fairly taught in the art prior to the making of the instant invention. Applicant has not identified the error in this showing. A single chain antibody, by definition, is composed of a first polypeptide, a VH chain, fused to a second polypeptide, a VL chain, in which the two polypeptides are expressed as a fusion protein. Nothing in the limitation of claim 1 excludes a single chain antibody of Ladner et al. from being encompassed by the term "first and second polypeptides which form heteromeric receptors, one or both of said polypeptides being expressed as fusion proteins on the surface of a cell". Since this is the only embodiment described

in the instant specification one assumes that it is encompassed by the claims. To use a surface expression system like the one described in the Ladner et al. reference in a binding protein generation system like that disclosed in the Huse et al. reference to reduce the effort required to identify a host organism carrying a DNA sequence encoding a protein having the desired binding characteristics would have been obvious to one of ordinary skill at the time of the instant invention.

Applicant has argued that "like claims 9-15, claims 1 and 16 similarly recite that the claimed cells and cloning system have or are derived from two vectors each having two pairs of restriction sites symmetrically oriented about a cloning site". Applicant is hereby expressly requested to identify the text in claim 1 which provides those elements referred to above.

15) Claims 6 to 8, 22 to 24, and 31 to 33 stand rejected under 35 U.S.C. § 103 as being unpatentable over the Huse et al. and Ladner et al. references as applied to claims 1 to 5, 16 to 21, and 25 to 30 above, and further in view of the Parmley et al. publication (GENE 73:305-318, 1988) for those reasons of record.. These claims further limit those above to the use of a filamentous bacteriophage vector which, as shown by the Parmley reference, were used routinely in the art prior to the instant invention to obtain the surface expression of binding proteins.

16) Claims 1 to 5 and 25 to 30 are rejected under 35 U.S.C. § 103 as being unpatentable over the Sastry et al. publication (P.N.A.S. 86:5728-5732, 1989) in view of the Ladner et al. (WO 88/06630, 1988) and Robinson et al. (WO 87/02671) publications for those reasons of record. Applicant has essentially traversed this rejection for those reasons as applied to the Huse et al. and Ladner et al. references above and those arguments were not found persuasive for those reasons given above.

17) Claims 6 to 8, 22 to 24, and 31 to 33 stand rejected under 35 U.S.C. § 103 as being unpatentable over the Sastry et al., Ladner et al., and Robinson et al. publications as applied to claims 1 to 5, 16 to 21, and 25 to 30 above, and further in view of the Parmley et al. reference (GENE 73:305-318, 1988) for those reasons of record.

Applicant's arguments filed 08 December of 1997 have been fully considered but they are not persuasive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (703) 308-4008. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached at (703) 308-2957.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JOHN ULM
PRIMARY EXAMINER
GROUP 1800